Rare Diseases Task Force

European Reference Networks in the Field of Rare Diseases:

State of the Art and Future Directions

Third Report

July 2008

I. Introduction

Due to the large number of rare diseases (RD), to their low individual prevalence, their severity, and to the scarcity of the information about each of them, the field of RD is one in which health needs faced by patients and their family is most acute. As such, it is also the field for which benefits of collaboration of expertise and maximisation of limited resources are most obvious.

As for all patients, the availability of expert local care for RD patients is ideal, but not always possible. The structure of such facilities implies a proximity to patients, limitation in patient capacity, and location in an area dependant on the patients' health care system for reimbursement purposes, or in a more distant area but within the framework of an agreement between centres for healthcare delivery. The complexity and chronic nature of RD requires multidisciplinary care and expertise that is often not available at the local level. But having to attend a clinic located in a foreign country can create several negative outcomes. Travelling to distant clinics requires patients to face an additional financial burden, obliging them to travel mostly at their own expense. Psychological burdens due to consultation in a foreign language and the lack of support when far way from family and community are possibly introduced. The cost of care may not be covered at all by health insurances from the country of origin. The global cost of care may be much greater than it would be in a local clinic, without significant benefit for the patient.

As such some Member States (MS) have identified hospitals throughout their respective countries that serve as physical expert structures for the management and care of RD patients at the national level; tackle rare diseases or other conditions requiring specialised care; serve as research and knowledge centres; update and contribute to the latest scientific knowledge; and treat patients mostly in a local catchment area, but also patients seeking care from other regions of the country. In some cases these centres are officially recognised as such and called *centres of reference, centres of expertise, reference centres, expert centres, centres of excellence, etc.* For the purposes of this and all future discussions they will be referred to as Centres of Expertise (CE).

The establishment of a CE for each rare disease in each MS is an unrealistic concept and the scarcity in the scientific community's knowledge of RD and the inadequate attention given to them by national competent authorities only further limits the abundance of such centres. As such, further collaboration at the European level in RD patient care is necessary.

The European Union is charged with responsibility of complementing, supporting, and adding value to the policies of the MS with the goal of encouraging healthcare systems based on solidarity, equality and accessibility and contributing to increased prosperity in the European Union by protecting and promoting human health and safety and by improving public health. Respecting the principle of subsidiarity and the responsibility of MS for the organisation and management of their health care systems, the creation of European Reference Networks (ERN) – physical or virtual networking of knowledge and expertise – can provide a high added-value for RD given the limited number of patients and scarcity of expertise at the national level despite the existence of CE.

Due to the varying definition of RD from MS to MS, differing healthcare structures, and different definitions of what constitutes a centre as a CE, a ERN consisting of individual CE will also reflect this variability[1]. Variability will additionally result from differences among the diseases in question, the experts involved (their expertise and interests) and the needs expressed by patient, researchers, and healthcare professionals. It is, therefore, very challenging to establish a common definition of an ERN and furthermore difficult to establish criteria of how to carefully select, create or assess ERN in a field where resources are limited.

In 2004, DG SANCO established the High Level Group on Health Services and Medical Care as a means of taking forward the recommendations made in the reflection process on patient mobility. One of the working groups of this High Level Group (HLG) is focussed on European Reference Networks (ERN)[2] and is chaired by the French Ministry of Health. This HLG Working Group on ERN has solicited contributions from Rare Disease Task Force (RDTF) regarding the discussion of ERN.

The RDTF published already two reports, in September 2005 and in March 2007, which can be retrieved for the RDTF website. These reports were used by the HLG to define its own analysis of the current situation and its proposition for the future. They were also instrumental in designing the call for proposals for pilot ERN.
The RDTF working group on Standards of care decided to continue exploring this issue as many concepts are still not stabilised. The current report is the result of the work done since the second report published in March 2007.

A preliminary Working Document was drafted by the scientific secretariat of the RDTF and served as a basis of discussion for the 5th Workshop on Centres of Expertise of the Standards of Care RDTF Working Group held in Paris in March 2008. This workshop served as an appropriate forum to discuss the definition, identification and assessment of ERN as all affected stakeholders are present (Annex 1). Conclusions of the discussion were incorporated into the preliminary report and validated by workshop participants. Finally, the report was sent to RDTF members and to coordinators of all EU funded networks in the field of rare diseases (Annex 2) for their contribution. Ultimately the recommendations in this document can serve to guide the actions concerning ERN at the Commission level.

II. Centres of Expertise

RD are severe, chronic, incapacitating diseases and require specialised, significant, and prolonged treatment. A CE for a rare disease or a group of rare diseases brings together a group of multidisciplinary hospital-based competences, organised around highly specialised medical teams.

The DG SANCO funded Rare Disease Task Force (RDTF) was charged with providing a report[3] on the current situation of CE in Europe to the High Level Group on Health Services and Medical Care Working Group on European Reference Networks. Their work revealed the following analysis.

[1] Centres of Reference for rare diseases in Europe: State-of-the-art in 2006 and recommendations of the Rare Diseases Task Force <http://ec.europa.eu/health/ph_threats/non_com/docs/contribution_policy.pdf>
[2] European networks of reference for rare diseases. <http://ec.europa.eu/health/ph_threats/non_com/rare_8_en.htm>
[3] Centres of Reference for rare diseases in Europe: State-of-the-art in 2006 and recommendations of the Rare Diseases Task Force <http://ec.europa.eu/health/ph_threats/non_com/docs/contribution_policy.pdf>

a. Definition of a Centre of Expertise in European countries

There is no common definition of what a CE is among MS which have established such centres. Even among countries with official CE, the definition of a rare disease varies between CE. The UK uses 1 in 50,000, Sweden and Denmark use 1 in 10,000 whereas France, Italy and Spain use the European orphan drugs regulation definition of 1 in 2,000. Regardless of the definition used, a large prevalence of diseases qualifying as rare exists in Europe.

The number and geographical distribution of centres in each country also varies though not proportionally to the size of the population, reflecting differences in the organisation of the health care systems.

Among the countries analysed thus far, seven countries use a national approach (Bulgaria, UK, Belgium, France Greece, Norway and the Netherlands), whereas others, such as Finland, Italy, Spain, and Sweden have a more regional. The majority of countries have not yet started to identify their expert centres.

The CE differ in form from one country to another:

- in form (reflecting the heterogeneity of national health systems)
- in focus (some CE specialise in one RD, some in several RD with similar needs, some on technologies shared across several RD)
- in the process used to identify, select and designate them (some have a specific policy regarding RD and have established CE in this framework (Bulgaria, Denmark, France, Italy, Sweden); some have established CE but not specifically for rare diseases (Belgium, Croatia, Czech Republic, Finland, Greece, Ireland, Portugal, Spain, UK); and some have no centres with these denominations, although they have centres with all characteristics of a CE (Austria, Cyprus, Estonia, Germany, Hungary, Latvia, Lithuania, Luxembourg, Netherlands, Poland, Romania, Serbia, Slovakia, Slovenia, Switzerland, Turkey).

b. Suggested Criteria Used to define a centre as Centre of Expertise

As agreed upon by HLG and the RDTF, the following criteria should define CE:

- appropriate capacities to diagnose, to do follow-up and manage patients with evidence of good outcomes when applicable
- attractiveness measured through the volume of activity which needs to be significantly larger than anticipated from the prevalence of the diseases and the catchment area, the catchment area being the loco-regional area normally served by the hosting hospital for non-rare diseases; or national coverage
- capacity to provide expert advice on diagnosis and management
- capacity to produce and adhere to good practice guidelines and to implement outcome measures and quality control
- demonstration of a multi-disciplinary approach

- high level of expertise and experience documented through publications, grants or honorific positions, teaching and training activities
- strong contribution to research
- close links and collaboration with other expert centres at national and international level and capacity to network

Additional publications on CE are listed in Annex 3.

c. The Added-value of Centres of Expertise

The reason for designating CE differs from one country to another. In principle, there are two main purposes for officially identifying specific resource centres. The first is to provide a rating scheme that enables consumers to identify the appropriate healthcare resource for their case. The overall objective of a rating scheme is to guide consumers to trustworthy health information and empower them to select high-quality services for referral. It is recommended that the same rating scheme be used in all MS.

The second purpose of designating CE is to enable healthcare managers to identify where best to allocate specific financial resources in order to support the additional activities linked to the duties of these centres. This is because designated centres have both rights and duties that require additional staff and resources. It is well established that the designation of a centre as a CE increases its referral rate and the number of requests for expert opinions. In addition, CE must be actively involved in clinical research, issue best practice guidelines and produce information leaflets for patients; all these activities require additional resources that can only be allocated by national authorities at the MS level.

d. Assessing Centres of Expertise

As most MS do not officially recognise CE within their healthcare systems, it is not yet possible to fully evaluate the varying experiences at the MS level. However, several MS recognising CE have established measures to assess the added-value of CE and their findings should be noted.

Denmark established two designated centres for rare diseases at the university hospital level in addition to 100 specialised clinics. The final selection is done by the National Board of Health after consultation of the learned societies, the administrations and patient organisations. In 2003, Rare Disorders Denmark, the Danish national rare disease alliance, carried out a survey among 900 people suffering from rare disorders to investigate the scope of health care offered to patients with rare disorders and their overall satisfaction with their course of treatment in CE. Although only 33% of RD patients reported being treated at a CE, those receiving care at a CE were more satisfied with their treatment and individual actions plans were a significant factor.

Within the English National Health System, there are two tiers of commissioning (planning, funding and monitoring) for specialised services. The determining factor is the specialist skills required rather than the rarity of the disease. The lower tier of specialised commissioning is determined by a definition set of specialised services available on the National Health System website. These services are commissioned by 10 bodies in England (the specialized commissioning groups) each responsible for a population of about 5 million people. The higher tier of national services is commissioned by the

National Commissioning Group. This tier includes procedures, medical and mental health services, and diagnostic services. The threshold for national commissioning is fewer than 1000 patients in England - equivalent to 0.2 per 10,000 population. Great emphasis is placed on monitoring clinical outcomes in the nationally commissioned services. Outcomes of surgery (for example portoenterostomy for biliary atresia) and other interventions (for example interventional radiology for malformation of the Vein of Galen, or gene therapy for immunodeficiency disorder) are monitored for all patients treated – a 100% consecutive case series. There is however difficulty in defining appropriate outcomes for some rare and untreatable disorders (for example epidermolysis bullosa and Alstrom syndrome). For the diagnostic services (for example primary ciliary dyskinesia) emphasis is placed on external inspection and accreditation (CPA) and external quality assurance systems (EQAS). There are separate health systems in Scotland, Wales and Northern Ireland.

France is the only MS to recognise CE within the framework of a national plan on RD. In France, CE apply annually through a competitive call for proposals. As of 2008, 132 CE have been established. Each centre is designated for five years, with a mid-term self evaluation after three years and an external evaluation after five years by one RD expert and one representative of the French National Authority for Health to determine renewal of funding.

As has been the experience in France, the success of such assessment strategies is contingent on the fact that it be disease-specific, centre-specific, and above all, specific to the healthcare system in question.

e. Recommendations

Given the variability of CE across Europe, networking activities and cooperation are one solution in the provision of the highest quality of services for the widest audience. As such, the RDTF Working Group on Standards of Care recommended in their report [4] that:

- MS having a policy for establishing national or regional CE for RD agree as much as possible on an operational definition of what is a CE and on how to designate them.
- MS with established CE should be encouraged to share their experience and the results of their outcome measures.
- MS not having a policy regarding the establishment of CE for rare diseases, find an appropriate way to organise their health care system to serve the needs of patients, either through the establishment of CE or through contracting with other CE abroad (not too distant if possible), and developing electronic communication between local clinics and CE from all over Europe.
- MS contribute to the identification of their expert centres and support them financially as much as possible
- MS organise healthcare pathways for their patients through the establishment of cooperation with all necessary expert centres from within the country and from abroad when necessary.

The RDTF Working Group on Standards of Care also recommended in their report that:

[4] Centres of Reference for rare diseases in Europe: State-of-the-art in 2006 and recommendations of the Rare Diseases Task Force <http://ec.europa.eu/health/ph_threats/non_com/docs/contribution_policy.pdf>

- the European Commission play an important role in promoting the identification of centres of expertise and in the diffusion of the information about them

These recommendations were agreed upon by all Workshop Participants (Annex 1).

III. European Reference Networks

The creation of European Reference Networks (ERN) – physical or virtual networking of knowledge and expertise – can provide a high added-value for RD given the limited number of patients and scarcity of expertise at the national level despite the existence of CE. Developing European collaboration for the delivery of health care and medical services in the field of RD has major potential in bringing benefits to European citizens by:

- overcoming the limited experience of professionals confronted with very rare conditions (including improved diagnosis, care, clinical research, and knowledge)
- improving access for EU citizens to treatment requiring a particular concentration/pooling of resources (infrastructure and knowledge) or expertise,
- offering patients the highest possible chance of success through sharing of expertise and resources,
- maximising cost-effective use of resources by concentrating them where appropriate,
- helping to share knowledge and provide training for health professionals,
- acting as benchmarks to help develop and spread best practice throughout Europe,
- providing to small countries with insufficient resources from their health care sector, a full range of highly specialised services of the highest quality.

Due to the varying definition of RD from MS to MS, differing healthcare structures, and different definitions of what constitutes a centre as a CE, ERN consisting of individual CE will also reflect this variability.
Variability will additionally result from differences among the diseases in question, the experts involved (their expertise and interests) and the needs expressed by patient, researchers, and healthcare professionals. It is, therefore, very challenging to establish a common definition of an ERN and furthermore difficult to establish criteria of how to carefully select, create or assess ERN in a field where resources are limited. It is possible, however, to distinguish in general between two possible types of networking activities: those that concern research and those that concern public health issues. In addition, funding for research and for public health policy making comes from different sources (DG Research and DG SANCO respectively). It is, therefore, logical to discuss these two types of networks separately with regards to their specific objectives, despite the fact that the CE are always mixed structure.

a. Structure of a European Reference Network

Whether it be for research or public health issues, on an abstract level, a network consists of nodes plus links between the nodes. A network is a European network when its nodes (CE) are located in more than one European country, though not necessarily every European country. The network encompasses the whole of Europe, because patients in every European country can benefit from the

network. The CE are the nodes, and the links between them are communications. Thus, a network of CE is characterised by communication between the CE in the network. These communications may be electronic or face-to-face (at a meeting or conference). Communication in the network will normally be from any node to all other nodes *i.e.* from one CE to all of the other CE. Occasionally communication may be private, from one centre to a subset of the other centres, but this will not be the norm. Communication may be needed to develop a consensus and CE are members of the network because they communicate in this way. CE which do not share ideas and opinions are not active members of the network. It is the sharing of expert opinion and ideas which provides the key benefit of the network. Within the network the nodes are equal; there is no hierarchy between CE, although one of them acts as coordinator on behalf of the others.

In summary, following characteristics of the ERN were agreed upon as guiding the discussion of ERN:

- Hierarchy between national or regional networks of CE should be avoided.
- Networking of CE should be favoured, rather than isolated CE.
- In principle, expertise should travel rather than patients themselves. However, it should be possible for patients to travel to CE when necessary.

b. Defining the Objectives: two types of networks

In reality, however, the structure of a ERN is not so simple. Networking in any field is the result of a voluntary collaboration of professional, each with different needs, preferences, expertise, and experience. Their partnership is an evolving process; the result of a history of successful cooperation and mutual understanding of future progress.

Research Networks

In the field of RD research, groups of professionals spanning several European MS agree to collaborate, and most apply for competitive funding through the Framework Programmes of DG Research[5].

An ERN focusing on research may:

- share data through the systematic collection of patient data
- establish repositories of biological samples
- share expertise for research purposes

Several projects funded under the DG Research Seventh Framework Programme illustrate such research networking activities.

The European Integrated Project on Spinocerebellar Ataxias (EUROSCA)[6] aims to develop an international standard on the clinical evaluation based on clinical rating scales, structural imaging, and electrophysiology. The creation of the European SCA Registry (EUROSCA-R) will ensure standardized data acquisition and facilitate continuous recruitment of SCA patients throughout

[5] A collection of existing RD networks funded by the EC has been created by Orphanet.
[6] The European Integrated Project on spinocerebellar ataxias. <http://www.eurosca.org/>

Europe for linkage analysis, identification of novel ataxia genes, natural history studies, and eventually genotype-phenotype correlations. This search for genetic modifier factors in SCA will allow a better comprehension of factors accounting for wide clinical variability with application for prognosis and to identify new potential targets (modifier genes) for delaying the age at onset or disease progression. EUROSCA will also implement strong research projects to generate and characterize cellular and transgenic models, which will allow a more defined study of the pathogenesis and will serve as a tool for first therapeutic studies. Training programs will complement research efforts and clinical work.

European Research Network for Alternating Hemiplegia (ENRAH)[7] aims to coordinate, support and promote educational and research activities in Alternating Hemiplegia in Childhood (AHC) by establishing a European multidisciplinary research network, setting up a web-based registry of AHC cases in Europe, identifying relevant SMEs and integrating them into the network's activities, and collecting project ideas and research profiles of SMEs working in AHC.

The Prader-Willi Syndrome: gene expression, obesity and mental health Specific Targeted Research Project[8] aims to integrate molecular biological studies and establish the basis for an EU wide clinical study of PWS. By establishing a standardised database, specifically designed for PWS, it will enable the collection of clinical data across the EU in a manner that will allow, in the future, the investigation of genetic and other influences on the development of people with PWS across all ages, thereby complementing the molecular biological studies that will identify the neurobiological mechanisms and signalling pathways that mediate between genotype and phenotype. The project will contribute to the understanding of early development and increase the comprehension of basic mechanisms responsible for obesity and severe psychotic illness in the general population. Given the high morbidity and mortality rate associated with having PWS, the project will provide the basis for clinical studies that will then establish a benchmark for early diagnosis as well as for best practice in the health and social care of people living with PWS. These findings will be disseminated through scientific and practice-based journals and in collaboration with the EU National PWS Associations who are partners in this study. Ultimately a model for the multidisciplinary investigation of other rare disorders in the EU may be developed.

Public Health Networks

Health care professionals spanning several MS may also collaborate to:

- share clinical experience to sort out difficult individual cases
- produce clinical guidelines based on their shared clinical experience
- produce information for patients or professionals in the form of a library of answers to frequent queries

Current developments in molecular diagnosis, imaging, video conferencing, robotics and communication are making virtual centres through networking a real possibility, allowing highly specialised care to be supported in remote locations.

[7] European Association for Research and Alternating Hemiplegia. <http://www.enrah.net>
[8] The Prader-Willi Syndrome: gene expression, obesity and mental health Specific Targeted Research Project.<http://www.pwseu.org.uk/>

The European Network of Centres of Expertise for Dysmorphology (DYSCERNE)[9] aims to raise standards for the diagnosis and best practices for care of dysmorphic syndromes through the creation of the Dysmorphology Diagnostic System. This system will enable clinicians in the network to electronically submit cases for diagnosis by uploading photographic images and results of investigations including imaging studies to a secure, searchable archive. Recommendations and opinions from the expert diagnostic panel will be collated and sent back to the referring clinician.

For other RD such as Cystic Fibrosis, considerable information about the disease exists, though not equally for all health professionals and patients all MS. In the framework of the European Centres of Reference Network for Cystic Fibrosis (ECORN-CF) project, collaborating partner-countries provide expert advice to their patients and care team members in their mother language on a local website. After translation of questions and answers in English they are published on a central website with open access for everybody who is interested in the topic. Thus, a transfer of knowledge and expertise throughout Europe will guarantee the same level of expert advice in all partner countries and avoid long travel to distant Cystic Fibrosis CE.

Still other networks focus on the establishment of standards of care and promote earlier diagnosis. To this end, the Patient Associations and Alpha1 International Registry (PAAIR) members collect and store cross sectional, prospective data on general health and disease-related items in an existing online database. The idea is to analyse the network's impact on the disorder's morbidity and mortality and early diagnosis. This will be achieve by comparing the standards of the centres already in the AIR network and the centres identified in the new EU countries with the requirements established by the HLG. The group will set up interaction between national patient and doctor/scientist bodies (AIR), to generate a model of doctor-patient interaction in three EU countries (the Netherlands, Italy and Germany).

As illustrated by the examples above, separate networks for specific RD or conditions (or groups of RD) ensure optimal focus of expertise as opposed to single networks for all RD or rare conditions.

If, indeed, a legal instrument is established to provide continuous support to ERN they can realistically be expected to:

- allow multi-centre clinical studies as well as partnership with pharmaceutical companies;
- provide shared research resources: databases, biological resources (DNA, RNA, tissues, cells), registries (harmonisation of standard operating procedures), international epidemiological surveillance and pharmacovigilance;
- be instrumental in promoting education and training activities. In partnership with patient organisation, they will provide information and communication outreach activities towards the public, but also the primary health care professionals in order to improve referrals and follow up. Training activities for health professionals includes staff exchanges, meetings and conferences to exchange best practices, harmonise processes and disseminate standards and guidelines;
- cooperate closely with patient organisations who should be actively involved in the management and evaluation of both CE and ERN as experts for the production of information

[9] A European Network of Centres of Expertise for Dysmorphology. <http://www.dyscerne.org/dysc/Home>

documents, guidelines for diagnostic and care, the choice of the research tools and clinical trials to be performed within the networks.

Agreement at the European level on the pathologies, technologies and techniques to be covered by ERN was considered necessary by the HLG, drawing on national experiences and existing lists as many Member States (MS) currently have expert clinics but not any designated CE. The priority areas should be determined on the basis of the following indicators:

- diagnosis (when the diagnosis is difficult and is necessary for informed clinical management, to prevent complications and to set up treatment)
- therapeutics and management when treatment requires expertise and specialised interventions
- outcome when patients are at high risk of developing severe complications or disability that could be prevented
- technology and therapeutic innovations.

c. Selection for funding of ERN and Assessment of ERN

Criteria for selecting ERN are set out above. Their application to specific situations, however, requires significant expertise and knowledge of the current international situation. The HLG and the RDTF each propose different schemes for such evaluations.

The HLG Working Group on ERN has also produced a Draft Procedure for the Identification and Development of ERN[10]. The draft procedure describes three proposals for the identification and development of ERN. The document proposed the modification of the current system of selection and describes two top down approaches in which a Committee of the MS on ERN (i.e. the current HLG Working Group on ERN) in close collaboration with the EC and competent national authorities, identifies ERN to be continuously supported by the EC.

The RDTF bases its proposal of selection and of evaluation on the reality of the previously funded pilot ERN and DG SANCO funded research networks. In this framework collaborations occur because of voluntary application. Although their application for funding occurs in a competitive way, it does not guarantee that the most appropriate CE are initially selected to join the network. These decisions occur between researchers because of acquaintance, similarity in needs and interests, and a history of working well together. Respecting the principle of subsidiarity and taking into account the reality of networking in the field of RD it seems that guaranteeing the best CE to network and apply for funding at the EC level will be difficult. Continued compliance with the selection criteria can also only be ensured of funding for such networking remains competitive.

IV. Conclusion

[10] Draft Procedure for the Identification and Development of ERN.
http://ec.europa.eu/health/ph_overview/co_operation/mobility/docs/highlevel_2006_007_a1_en.pdf

Given the variability of health systems in each country involved, differing definitions of RD in each MS, and varying focuses of CE as a result of expertise of coordinators and needs of patients, it is difficult to suggest a unique structure for all possible ERN.

The DG SANCO-funded European Reference Network Pilot Projects [11] provide an opportunity to assess the relevance of the procedures and criteria proposed[12] by the HLG Working Group on ERN and the RDTF. The HLG Working Group on ERN has produced Draft questions[13] for each project leader of the pilot ERN projects. Analysis using these questions is anticipated to be carried out in two steps in which project leaders first provide provisional answers to questions concerning the preliminary stages of the establishment of their networks and then complete answers once the projects were complete or sufficiently progressed that practical experience was gained. Until a more thorough analysis of the experience of the Pilot Networks is possible, questions that remain include:

- How can the ERN of highest quality be selected?
- How will CE be selected as members of the ERN?
- Will the designation of a few ERN introduce a limitation when other successful networks also exist?
- How can a new instrument to ensure long-term funding be agreed upon while keeping the spirit of high quality research through a competitive application process?
- How do we ensure that selected networks truly comply with agreed criteria on a long-term basis?
- Who will address new questions and obstacles that arise from such pan-European collaborations such as the question of medical liability in virtual clinics?

Finally, direct indicators to measure the European added-value of ERN must be specifically identified for each type of network. It should be recognized that these indicators may change according to the experience of the DG SANCO pilot projects and other existing networks in the field of RD and could be different for each ERN.

The current recommendations of the RDTF for the European Commission include that it:

- continues its financial support networking of centres of expertise in the field of RD until an evaluation of the output of the networking process demonstrates that it is not cost-effective (which is extremely unlikely)
- opens its call for proposals to the definition of a methodology to assess the benefit of such networks from the perspective of the different stakeholders
- encourages, by all possible means, the development of electronic tools necessary for the development of telemedicine in the field of rare diseases.
- encourages the production of legal and ethical guidelines for participants of any European network involving patients
- with the cooperation of clinicians, patients, network coordinators, MS health authorities reconsiders the assessment of the added-value of ERN after:

[11] DG SANCO – Public Health, European Reference Network pilot projects. <http://ec.europa.eu/health/ph_threats/non_com/rare_8_en.htm#4>

[12] Draft Procedure for the Identification and Development of ERN. <http://ec.europa.eu/health/ph_overview/co_operation/mobility/docs/highlevel_2006_007_a1_en.pdf>

[13] HLG/COR/2007/5 REV1 Draft set of questions for each project leader of the pilot projects on European reference networks

- Additional findings from the experience of the pilot projects[14]
- Learning from the experience of existing collaborations in the field of RD (Annex 2)
- Continued identification of CE across Europe

[14] DG SANCO – Public Health, European Reference Network pilot projects. <http://ec.europa.eu/health/ph_threats/non_com/rare_8_en.htm#4>

Annex 1

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RDTF Workshop: Assessing the Added-Value of European Reference Networks
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Annex 2
Existing Networks in the Field of Rare Diseases

- Curing autoimmune disease; a translational approach to autoimmune diseases in the post-genomic era using inflammatory arthritis and myositis as prototypes and learning examples (AUTOCURE)
- Paraneoplastic Neurological Syndromes (PNS) strengthening the European network (PNS-EURONET2)
- European Renal Genome Project (EUREGENE)
- Using European and international populations to identify autism susceptibility loci (AUTISM MOLGEN)
- Control of Intracellular Calcium in Arrhythmias (CONTICA)
- European Coordination Action for Research in Cystic Fibrosis (EUROCARECF)
- Integrated project to decipher the biological function of peroxisomes in health and disease (PEROXISOMES)
- Congenital disorders of glycosylation: a European network for the advancement of research, diagnosis and treatment of a growing group of rare disorders (EUROGLYCANET)
- Neuroprotective strategies for multiple sclerosis (NEUROPROMISE)
- Functional genomics of the retina in health and disease (EVI-GENORET)
- Adult mesenchymal stem cells engineering for connective tissue disorders. From the bench to the bed side (GENOSTEM)
- Rational Treatment Strategies Combating Mitochondrial Oxidative Phosphorylation (OXPHOS) Disorders (EUMITOCOMBAT)
- NOVEL APPROACHES TO PATHOGENESIS, DIAGNOSIS AND TREATMENT OF AUTOIMMUNE DISEASES BASED ON NEW INSIGHTS INTO THYMUS-DEPENDENT SELF-TOLERANCE (EURO-THYMAIDE)
- Genetics of coenzyme Q deficiency in humans (UBIGENES)
- Improved precision of nucleic acid based therapy of cystic fibrosis (IMPROVED PRECISION)
- Concerted Safety & Efficiency Evaluation of Retroviral Transgenesis in Gene Therapy of Inherited Diseases (CONSERT)
- An integrated immunological and cellular strategy for sensitive TSE diagnosis and strain discrimination (TSEUR)
- Pulmonary Hypertension: Functional Genomics and Therapy of Lung Vascular Remodelling (PULMOTENSION)
- Neutralizing antibodies on Interferon beta in Multiple Sclerosis (NABINMS)
- Development and application of transposons and site-specific integration technologies as non-viral gene delivery methods for ex vivo gene-based therapies (INTHER)
- From molecules to networks: understanding synaptic physiology and pathology of the brain through mouse models (EUSYNAPSE)
- Nuclear Envelope-linked Rare Human Diseases: From Molecular Pathophysiology towards Clinical Applications (EURO-LAMINOPATHIES)
- Ex vivo gene delivery for stem cells of clinical interests using synthetic processes of cellular and nuclear import and targeted chromosomal integration (SYNTHEGENEDELIVERY)
- Prevention, diagnosis and molecular characterisation of mismatch repair defect-related hereditary cancers of the digestive system (MMR-RELATED CANCER)
- Normal and abnormal cardiac excitation: generation, propagation, and coupling to contraction (NORMACOR)
- European network to promote research into uncommon cancers in adults and children: Pathology, Biology and Genetics of Bone Tumours (EUROBONET)
- Combined isolation and stable non-viral transfection of hematopoietic cells- a novel platform technology for ex vivo hematopoietic stem cell gene therapy (MAGSELECTOFECTION)
- Biocompatible non-viral polymeric gene delivery systems for the ex vivo treatment of ocular and cardiovascular diseases with high unmet medical need (POLEXGENE)
- Mitochondrial diseases: From bedside to genome to bedside (MITOCIRCLE)
- Autoimmune polyendocrine syndrome type I - a rare disorder of childhood as a model for autoimmunity (EURAPS)
- CONnective TIssue CAncers NETwork to integrate European Experience in Adults and Children (CONTICANET)
- Insights into novel therapeutic strategies for a nuclear inclusion disease caused by polyalanine expansion (POLYALA)
- Ovarian Cancer - Diagnosing a Silent Killer (OVCAD)
- PROgnosis and THerapeutic targets in the "Ewing" family of TumourS (PROTHETS)
- Strengthen and develop scientific and technological excellence in research and therapy of leukemia (CML, AML, ALL, CLL, MDS, CMPD) by integration of the leading national leukemia networks and their interdisciplinary partner groups in Europe (EUROPEAN LEUKEMIANET)

- Special Non-Invasive Advances in Foetal and Neonatal Evaluation Network (SAFE)
- European integrated project on spinocerebellar ataxias: Pathogenesis, genetics, animal models and therapy (EUROSCA)
- Wilson Disease: Creating a European Clinical Database and designing multicentre randomised controlled clinical trials EUROWILSON (EUROCOPPER)
- CELLS INTO ORGANS: FUNCTIONAL GENOMICS FOR DEVELOPMENT AND DISEASE OF MESODERMAL ORGAN SYSTEMS (CELLS INTO ORGANS)
- European Consortium for Stem Cell Research (EUROSTEMCELL)
- Episomal vectors as gene delivery systems for therapeutic application (EPI-VECTOR)
- Molecular optimization of laser/electrotransfer DNA administration into muscle and skin for gene therapy (MOLEDA)
- Genetic testing in Europe - network for test development harmonization, validation and standardization of services (EUROGENTEST)
- Development of new methodologies for low abundance proteomics: application to cystic fibrosis (NEUPROCF)
- Ex vivo gene therapy for recessive dystrophic epidermlysis bullosa: pre-clinical and clinical studies (THERAPEUSKIN)
- Gene therapy for Epidermolysis Bullosa: a model system for treatment of inherited skin diseases (SKINTHERAPY)
- Rare genetic skin disease: advancing diagnosis, management and awareness through a European network (GENESKIN)
- DNA electrotransfer of plasmids coding for antiangiogenic factors as a proof of principle of non-viral gene therapy for the treatment of skin disease (ANGIOSKIN)
- Prader-Willi syndrom: a model linking gene expression, obesity and mental health (PWS)
- From stem cell technology to functional restoration after spinal cord injury (RESCUE)
- Multi-organismic approach to study normal and aberrant muscle development, function and repair (MYORES)
- Molecular mechanisms of neuronal degeneration: from cell biology to the clinic (NEURONE)
- Advances in hearing science: from functional genomics to therapies (EUROHEAR)
- ERA-Net for research programmes on rare diseases (E-Rare)
- RDTF - Scientific secretariat of the Rare Disease Task Force (RDTF)
- European Network For Rare And Congenital Anaemias (ENERCA)
- European Myasthenia Gravis Network (EUROMYASTHENIA)
- European Autism Information System (EAIS)
- Rare Disease Patient Solidarity RAPSODY
- Towards the development of an effective enzyme replacement therapy for human alpha- mannosidosis (HUE-MAN)
- Novel molecular diagnostic tools for the prevention and diagnosis of pancreatic cancer (MOLDIAG-PACA)
- Development of a pre-clinical blood test for prion diseases (ANTEPRION)
- Translational research in Europe - Assessment and treatment of neuromuscular diseases (TREAT-NMD)
- Genetic control of the pathogenesis of diseases based on iron accumulation (EUROIRON1)
- Embryonic stem cells for therapy and exploration of mechanisms in Huntington disease (STEM-HD)
- Chimaeric T-cells for the treatment of paediatric cancers (CHILDHOPE)
- Selecting and validating drug targets from the human kinome for high risk pediatric cancers (KIDSCANCERKINOME)
- Soft tissue engineering for congenital birth defects in children: new treatment modalities for spina bifida, urogenital and abdominal wall defects (EUROSTEC)
- Amplification of human myogenic stem cells in clinical conditions (MYOAMP)
- Systemic Amyloidoses in Europe (EURAMY)
- Development of models to improve management of Myasthenia Gravis: From basic knowledge to clinical application (MYASTAID)
- Small ligands to interfere with Thymidylate synthase dimer formation as new tools for development of anticancer agents against ovarian carcinoma (LIGHTS)
- Development of novel management strategies for invasive aspergillosis (MANASP)
- Identification of early disease markers, novel pharmacologically tractable targets and small molecule phenotypic modulators in Huntington's Disease' (TAMAHUD)
- Pathophysiology of the cartilage growth plate (EUROGROW)
- Diamond to retina artificial micro-interface structures (DREAMS)
- Prevention, control and management of prion diseases (NEUROPRION)

Annex 3
Publications about Centres of Expertise and European Reference Networks

European Organisation for Rare Centres of Expertise and European Reference Networks for Rare Diseases. Eurordis Specific Contribution to the Public Consultation: "Rare Diseases: Europe's Challenges". February, 2008

European Commission Health and Consumer Protection Directorate-General (DG SANCO). High Level Group on health services and medical care. Report on the work of the High Level Group in 2007. November 26, 2007.

European Commission Health and Consumer Protection Directorate-General (DG SANCO). High Level Group on health services and medical care. Report on the work of the High Level Group in 2006. October 10, 2006.

European Commission Health and Consumer Protection Directorate-General (DG SANCO). High Level Group on health services and medical care. Report on the work of the High Level Group in 2005. November 18, 2005.

Rare Disease Task Force. Centres of Reference for rare diseases in Europe: State of the Art in 2006 and Recommendations of the Rare Diseases Task Force. March, 2007

Rare Disease Task Force. Overview of Current Centres of Reference on Rare Diseases in the EU. September, 2005